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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/335,461	11/07/94	GIERSET	R

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EXAMINER	
LOW, C	
ART UNIT	**PAPER NUMBER**
1804	11

DATE MAILED: 11/12/96

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

See the attached Sheets.

Attachments:
PTO-303
PTOL-413

Christopher S. F. Low

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800

Advisory Action

Application No.	Applicant(s)
08/335,461	Gjerset et al.
Examiner	**Group Art Unit**
Christopher S. F. Low	1804

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☐ expires _____ months from the mailing date of the final rejection.

b) ☐ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☒ Appellant's Brief is due two months from the date of the Notice of Appeal filed on *24 Oct 1996* (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *24 Oct 1996* has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:

☒ The proposed amendment(s):

☐ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☒ will not be entered because:

☒ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☒ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: *Claims 21 and 22 (two claims) are to be canceled, however, five (5) new claims are added. New claim 27 adds limitations to the genes not previously present in any claim nor present in any claim as originally filed.*

☒ Applicant's response has overcome the following rejection(s):
None.

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:
The reasons are as indicated in the prior Office Action. The amendments in the above indicated response have not been entered.

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: *none*

Claims objected to: _____

Claims rejected: *1-23 as indicated in the prior Office Action*

☐ The proposed drawing correction filed on _____ ☐ has ☐ has not been approved by the Examiner.

☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ .

☐ Other

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ART UNIT 1804

The amendment and comments in the response after final filed 24 October 1996 have been considered but has not been entered as noted on the attached PTO-303.

The comments (applicant's response at pages 8-13) regarding the rejections under 35 U.S.C. 112 first and second paragraphs are not persuasive for the reasons indicated in the prior Office Actions and because the amendment to the claims is not entered. As previously discussed, the instant rejection under 35 U.S.C. 112 first paragraph is made and applied under 35 U.S.C. 112. Contrary to the allegation in the response after final, this is not a rejection under 35 U.S.C. 101. The allegations in the response of doubts as to utility are not doubts of utility, i.e., usefulness, but expressions that lead the skilled in the art as to how to use the invention as set forth in the claims. These are not the examiner's expressions of doubt but doubts of others extremely skilled in the art. The Guidelines that applicant's response refer to are those for 35 U.S.C. 101. Contrary to the allegations in the response, 35 U.S.C. 101 is not 35 U.S.C. 112 first paragraph.

As to the discussion of the Roth *et al.* reference, said reference is not applicant, nor applicant's disclosure, nor does it appear to refer to applicant's disclosure. The Roth *et al.* reference is published after applicant's filing, does not establish the state of the art prior to or at the time of filing of the present application. This, it cannot be used to describe or enable the present application. The references to Moi *et al.* and Aebi *et al.* have also been considered as to the assertion of limitation to the p53 gene, however, the comments are not persuasive. Neither the genes disclosed in the reference do not appear to be disclosed in the present application. What is not disclosed is not described. What is not described is not enabled nor does the present application indicate how to find nor use the genes recited in the references. See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991).

The comments in the present response are not persuasive as to the rejections under 35 U.S.C. 103 which remain for the reasons indicated in the prior Office Actions. The claims are directed to replacing a wildtype p53 gene into a cell which contains no or a defective p53 gene to sensitize the cell to cancer therapy. The combined cited prior art disclosed that wildtype p53 genes have been inserted into tumor cells, that tumor burden is lowered, and that other therapies are known

to be combined with genetic therapy. Here, putting the same gene into a cancer cell is expected to have the same results, not different results. Thus, the comments in the response (pages 14-20) are not persuasive. It is also noted that applicant's response asserts no motivation, however, the comments are not persuasive because it would have been obvious to one of ordinary skill in the art to combine the teachings of Cheng *et al.* (Cancer Res.) taken with Srivastava (US '749), Moossa *et al.* with Wu *et al.*, Malkin *et al.* and Chen *et al.* for treatment of cancer and directed delivery of the DNA encoding for example p53 to effect reduced tumorigenicity and reduced frequency of posttransplantation relapse.

The citation of the *In re Gulack, In re Fine, In re Laskowski, In re Dow Chemical Co.*, and *Lindemann Machinenfabrik v. American Hoist & Derrick Co.* decisions are noted, however, they are not persuasive because the invention has been considered as a whole as has the cited prior art. The cited prior art disclosed that wildtype p53 genes have been inserted into tumor cells, that tumor burden is lowered, and that other therapies are known to be combined with genetic therapy. Here, putting the same gene into a cancer cell is expected to have the same results, not different results. As pointed out in the stated grounds of rejection and as indicated above there are reasons that motivate one of ordinary skill in the art to combine the references and to combine therapies which reasons and motivation are founded in the cited prior art. There is no reference to applicant's disclosure. Thus, the assertion in the response is wrong. The discussion of unexpected results (pages 19-20) is, contrary to the comments in the response, expected since it would have been obvious to any one of ordinary skill in the art that radiation therapy (as for example Moossa *et al.* at pages 477, 1138, 1140, and 1170), chemotherapy (as for example Moossa *et al.* at pages 527-536, 565-568, 1098, 1140, and 1572), biological therapy (as for example Moossa *et al.* at pages 607-612 using biological response modifiers), cryotherapy (as for example Moossa *et al.* at pages 1098, 1170, 1329, 1368, and 1569-1570), and hyperthermia (as for example Moossa *et al.* at page 1139-1149) are known treatment methods that have been successfully used and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations. One would have used known routine methods for delivery of the therapeutic agent (as for example via an artery (page 590) or a (page 591) body cavity or by IV as for example indicated at page 592) and would have resulted in the process wherein a DNA encoding a tumor sensitizing product would have

been delivered to an afflicted individual along with routine known and established appropriate therapies (radiation therapy, chemotherapy, biological therapy, cryotherapy, and hyperthermia therapy in one or more combinations) for treatment of cancers. Moreover, the Cheng *et al.* reference disclosed suppression of T-cell acute lymphoblastic leukemia (T-ALL) post transfection of T-ALL cells with a vector that effects expression of the p53 gene product (see at least the abstract) and suggest such treatment for therapeutic suppression of the unregulated growth of T-ALL cells by introduction of the DNA encoding p53 into cells in conjunction with autologous bone marrow transplantation regimes in an effort to reduce the frequency of posttransplantation relapse and at page 225, the teaching that expression of the wild-type allele for p53 effected a "powerful suppression of the tumorigenic phenotype *in vivo* (i.e., a correlation of the effects) without evidence of significant toxic effects in the cells. Here, where Cheng *et al.* indicate use of vectors to provide the DNA encoding wild-type p53, it would have been obvious to one of ordinary skill in the art to have used known vectors and processes demonstrated as effective that are known to function *in vivo* for delivery of known DNA encoding wild-type p53 wherein Srivastava discloses vectors that are indicated as safe for gene therapy (i.e., reduction/elimination of a factor in the potential problem of heterologous DNA effecting unwanted effects which also would have motivated one of ordinary skill in the art to have used the teachings and vectors and modifications thereto such as disclosed in the Srivastava '749 patent which at col 3 indicates the vectors are for bone marrow cells, i.e., like those of the Cheng *et al.* reference) and to have used virus such as an adeno, herpes, or vaccinia virus (see col 3) for delivery of DNA encoding, for example, p53 for treatment of cancer (col 6). Thus, where the gene has been delivered to the cells, it is expected that the same gene has the same effects. Thus, one would expect increased tumor cell killing (i.e., sensitivity to treatments) since there is decreased tumor burden and tumor suppression. Thus, the comments in the response are not persuasive.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Low whose telephone number is (703) 308-2923. Inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1) and must conform to the notice published in the Official Gazette, 1096 OG 30 (15 November 1989). The telephone number assigned to Art Unit 1804 in the CM1 PTO Fax Center is (703) 308-0294.

CSFL
8 November 1996

Christopher S. F. Low

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GROUP 1800